# Vaccines

## Introduction

This lesson covers the long-lasting immunity conferred by memory cells—how it happens and why it's good that it does. We approach this from the perspective of B cells and antibodies because it's conceptually easier to understand than T cells. However, memory cells exist for both cell lines. Our example will be the disease tetanus. We chose tetanus because of how powerful a message this example sends. The dose at which the tetanus toxin kills a person (the toxic dose) is far less than the dose needed for the body to recognize it as foreign and initiate an immune response (the immunogenic dose). The vaccine (a toxoid) has all the bits of the toxin that help our body mount an immune response to the toxin, meaning to train our B cells to recognize the toxin at a subsequent exposure. The cool thing is that the vaccine (a toxoid) has none of the toxic bits and only the immunogenic bits.

Tetanus is also a very heavily tested topic. We'll explain what all those words in the parentheses of the paragraph above mean by the end of this lesson.

Pathogens are the bugs. Our immune system fights pathogens. Antigens are part of the bugs, pieces of the pathogen that our immune system recognizes. Antigens are the thing our immune system recognizes, that cause it to initiate the immune response. Pathogen and antigen are usually used interchangeably, because for all intents and purposes for our immune system, they mean the same thing. But a toxin is an antigen secreted by a pathogen, the toxin being the part that causes the disease.

## Setting Up Some Vocabulary on Immunity

Immunity is either active or passive, and either natural or artificial. Active means the body makes its own antibodies. Passive means the body doesn't make them. Natural means immunity's gained via infection. Artificial means something was injected—a vaccine if active (because the immune system responds by making antibodies), antibody if passive (because the immune system doesn't need to make the antibodies, they are provided for it).

**Passive** immunity means the organism receiving the immunity is **not making its own** antibodies, which are thus said to be exogenous. The utility of passive immunity is that because the organism doesn't have to make them, they're **immediately available** and confer **instant immunity**. The problem with that, however, is that the immune system doesn't learn and can't fight on subsequent exposure, and the immunity doesn't last long. If there's a chance that a patient has tetanus, and isn't vaccinated, it's a good idea to confer temporary immunity with intravenous immunoglobulin (a dose of antibody), passive immunity.

**Active** immunity means the organism receiving immunity **is making its own** antibodies, and these antibodies are said to be endogenous. The utility here is that the organism **learns** and makes **memory cells** so that this confers a **long-lasting immunity**. The problem with this method is that it takes **time to mount** the response. To not need IVIg against tetanus, we give people vaccines long before the first exposure, so that when they are finally exposed, their own immune system can mount a faster and stronger immune response (more on this in the next section).

Natural and artificial are poorly chosen names because of the connotation that one is better. **Natural** means "human made it." Examples of natural immunity are IgG crossing the placenta (natural and passive) or by becoming infected in order to get immunity (chickenpox parties would be natural and active). **Artificial** means "we injected it." There's nothing wrong with artificial immunity. In fact, **artificial immunity** (aka **vaccines**) is the preferred method of conferring immunity, as they don't require one actually to become sick or symptomatic with the disease we are protecting against. Vaccines don't cause autism. They prevent disease. Vaccines spare children from the scars that chickenpox can bring

and also from reactivation later on in life as shingles. If we vaccinate against chickenpox, we'll never see chickenpox or shingles ever again. We'd also like to drop the "natural vs. artificial" and call it "exposed-infection" and "unexposed-administered."

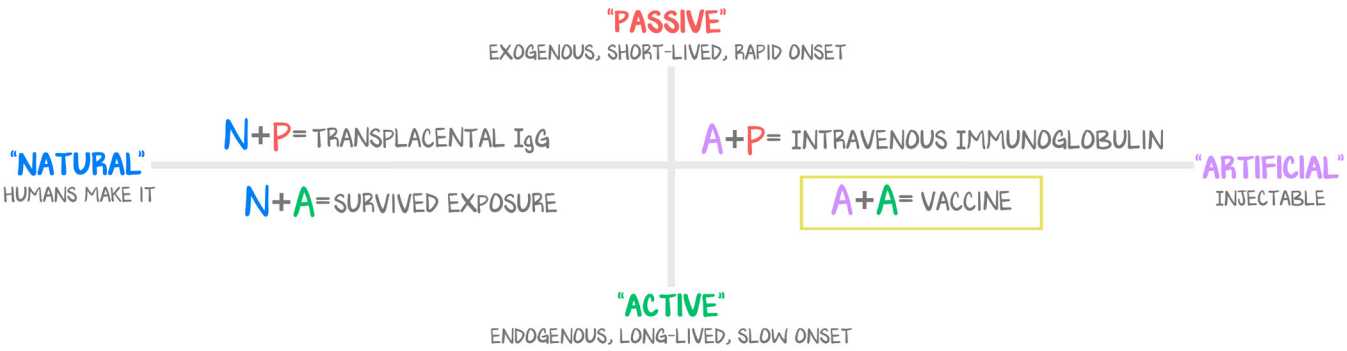


**Figure 13.1: Vocabulary and Examples**
IgG crossing the placenta confers natural but passive immunity. These IgGs last for about six months and use mom's antibodies to keep baby from getting sick. Purposefully infecting yourself to obtain immunity is natural and active. Providing IVIg during an acute tetanus infection binds up the toxin so the patient doesn't die. That is passive and artificial. All vaccines are active and artificial.

Now consider tetanus. Any attempt to confer immunity through exposure, that is, for a nonvaccinated person to purposely self-inoculate with tetanus toxin, would kill that person. The **dose of tetanus that kills is less than the dose that would confer immunity**. However, because the toxoid has none of the active properties of the toxin, the toxoid vaccine can be given in sufficiently high dose to provoke an immune response. Receiving **the toxoid vaccine** allows the body to remember the tetanus antigen so that the body can create a robust immune response when the real tetanus toxin is encountered. When the immune system already recognizes the toxin (by being trained by the toxoid) the person **doesn't get the disease at all** and simply eliminates any toxin.

Let's look at why in the next section.

## Primary and Secondary Immune Response

The **primary immune response** is what happens the **first time** an antigen is encountered, called the **primary exposure**. When an antigen is encountered for the first time, the innate immune system fights that antigen. Antigens are usually part of pathogens, and so by fighting the antigen, the immune system is fighting the pathogen. It also sends APCs to secondary lymphoid organs to present those antigens to the adaptive immune system. T-helper cells secrete cytokines in response to whatever information the APC has brought back, ensuring that both the adaptive and innate immune system work better against that antigen. T-helper cells can activate cytotoxic T cells, which kill enemy pathogens and promote cellular immunity through their own cytokines. T-helper cells can activate B cells, inducing them to proliferate and secrete antibodies to improve phagocytosis (opsonization), neutralize pathogens, and increase complement activation. Antibody immunity starts as a **first wave of IgM-secreting plasma cells**—low-affinity less-effective antibodies—called the **primary antibody response.** This takes time to initiate, is slower and weaker, and has less affinity than the secondary antibody response. This is because the naive mature B cell has a nonspecific immunoglobulin. It must find the antigen, ask for permission from the veteran T cell, remove its probationary card, and go through somatic hypermutation, affinity maturation, and isotype switching. A primary antibody response takes **over 7 days from the time of exposure to the production of IgG antibodies**. In the meantime, plasma cells are secreting the IgM of the original immunoglobulin. The lack of specificity and all that time to mount a meager response is why tetanus toxin kills a human before the immune response can happen.

That first exposure requires large doses of the antigen because the response is by a nonspecific IgM. But that first exposure ends with **memory cells**. B cells with the somatic hypermutated, isotype switched, affinity maturated immunoglobulin-as-surface-receptors now have a hyperspecificity to that antigen. The affinity for the antigen is significantly higher than it was during wave 1. The **next time** that antigen is encountered, the **secondary immune response** is set off. The secondary immune system is **faster** (no need for costimulation, approval of the probationary IgD, isotype switching) and **stronger** (because the higher the memory cell's receptor-immunoglobulin's affinity for the antigen, the more antibody gets made from the plasma cells that come from that memory cell), and also has a **higher specificity**, which really means that **lower concentrations of antigen are required to induce the response.** A secondary antibody response **takes about four days from exposure to the production of IgG antibodies,** there will be more immunoglobulins, and those immunoglobulins will have the highest affinity for the antigen.

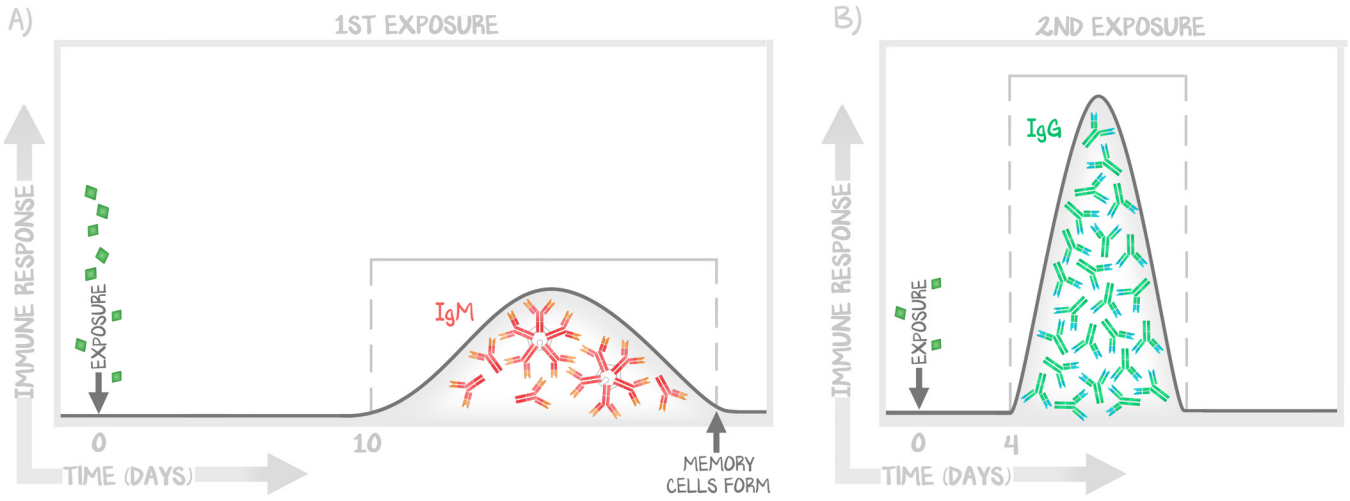


**Figure 13.2: Primary and Secondary Antibody Response**
The primary antibody response takes longer, is less specific, is not as strong, and requires increased dosages of antigen to be triggered. The secondary antibody response is faster, stronger, more specific, and requires significantly less antigen to initiate an immune response.

After the first exposure, with the creation of memory cells, a person becomes exposed-immune. As long as those memory cells persist, the host remains immune.

**Vaccination** essentially makes inoculation the initial exposure, rather than an infection. That is, they **induce primary immune response without infection**, but still get all the benefits of being immune.

## Antigenicity and Immunogenicity

In clinical medicine we use antigenicity and immunogenicity interchangeably, but in immunology they aren't the same. **Antigenicity** is the ability of an antigen to bind to an antibody. **Immunogenicity** is the ability of an antigen to induce an immune response. What we really care about is immunogenicity.

The dose of antigen required to provoke an immune response (that is, the dose required to be immunogenic) on first exposure is much higher than the dose required on repeat exposure. This should make intuitive sense—the first time an antigen is found, the IgM is just not specific for that antigen, so the B cell with the IgM-as-a-receptor needs more of the antigen to start the adaptive immune response. But after the first exposure, the memory cells have a highly specific antigen-binding portion (Fab) for that antigen on their immunoglobulin, so that smaller amounts will activate the IgG-as-a-receptor.

## Tetanus Vaccine

Tetanospasmin is a **toxin** made by the bacterium *C. tetani*, and causes the disease tetanus. The **lethal dose of the toxin is LESS THAN the immunogenic dose of toxin**. That means, in the case of tetanus, you **can't become exposed-immune**; exposure to the toxin would kill you before the immune response could defeat the antigen, let alone before the development of memory cells. Even if you survived the exposure, the **dose of exposure** is **insufficient** to achieve immunity.

In summary, if you don't get vaccinated against tetanus, you can't become immune. Period. If infected, you would die. If you are infected but don't die, you still won't be immune to another exposure. You will have to be immunized to have long-lasting immunity.

In the case of tetanus vaccine, we administer a **toxoid**. The toxoid (-oid) looks like the toxin, but doesn't do toxin things. The **antigenic portion** is retained, but the **toxic portion removed**. That means we can give HUGE doses of the toxoid (the antigen that looks just like the toxin) without any consequence to the patient. Both the toxoid and toxin require large doses to achieve immunogenicity. The toxoid at this dose is innocuous. The toxin at this dose would have killed the patient 20 times over.

The tetanus vaccine permits **active immunity**—it trains the immune system against the antigen by presenting the toxoid at immunogenic doses such that an immune response occurs. When the body encounters the toxin on "re-exposure," antibodies are already made, which neutralize the toxin.

Because **memory cells don't always last forever**, some antigens require repeating the exposure with the vaccine. This repetition acts as a **booster** to the immune system—reminding it of the antigen, priming memory cells, and increasing the vigorousness of a repeat exposure. This is why we need three tetanus vaccinations in life.

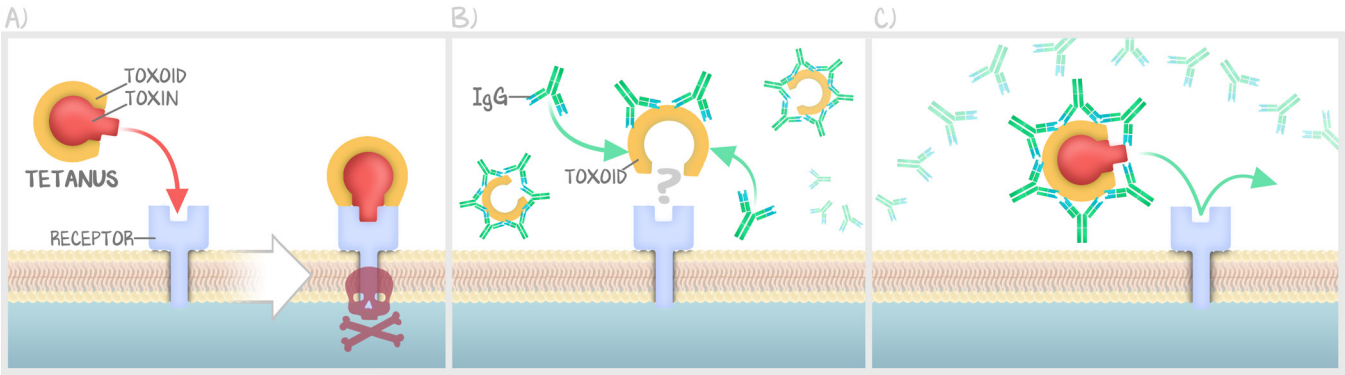


**Figure 13.3: Toxins and Toxoids**
(a) If the tetanus toxin combines with its receptor, the host dies. No immunity and no life. (b) If the toxoid is given, with the active part removed, the receptor isn't activated, and no disease happens. However, the toxoid is just as immunogenic as the toxin, and with too small a dose, immunity won't occur. But because the toxoid doesn't activate the receptor to cause disease, it can be given in large enough doses safely to elicit the immune response, so that (c) on re-exposure, memory cells will rapidly identify the antigen and mount the secondary antibody response.

## Tetanus Treatment

A dirty wound and no history of vaccinations leaves no hope of a natural immune response. The lethal dose is less than the immunogenic dose. The patient will die. Protect them **immediately with IVIg** and then **vaccinate with toxoid vaccine** against future exposure.

A dirty wound on someone who's had a vaccine, but it was a long time ago, will provoke a life-saving immune response. But a booster is recommended, so **give the toxoid vaccine.**

If the wound isn't dirty (no risk for tetanus), or the patient's had three vaccinations total, or the last dose was within 5 years, the **secondary immune response** is sufficient to protect against tetanus, and so neither the toxoid nor the IVIg is needed.

| TREATMENT OF A DIRTY WOUND (TETANUS POSSIBLE) | | |
|---|---|---|
| 3 total vaccines and<br>last vaccination < **5** years ago | 3 total vaccines but<br>last vaccination > **5** years ago | Incomplete vaccination series |
| No treatment needed | Toxoid only (booster) | **IVIg** and toxoid |

| TREATMENT OF A CLEAN WOUND (TETANUS NOT LIKELY) | | |
|---|---|---|
| 3 total vaccines and<br>last vaccination < **10** years ago | 3 total vaccines but<br>last vaccination > **10** years ago | Incomplete vaccination series |
| No treatment needed | Toxoid only (booster) | Toxoid only |

**Table 13.1: Comparing Treatment for Tetanus in Clean Wounds Versus Dirty Wounds**
The only difference in the treatment is highlighted in bold. Clean wounds get 10 years instead of 5. The only time IVIg is used is in a high-risk wound in a patient without vaccination. Note that a "complete" series is at least 3 doses of tetanus in a lifetime. The CDC still recommends a booster every 10 years.

## Types of Vaccines

**Live attenuated vaccines** usually contain **viral organisms**. These are still-active, living viruses, but are attenuated, or weak. Immunocompromised hosts should avoid them because they can still cause clinical disease. MMR, VZV, polio, yellow fever, and smallpox are examples.

**Killed vaccines** are dead. Often denatured by heat or chemical, they are therefore less immunogenic because of the denaturing that has occurred. This means repeated doses are often required to achieve immunity. Rabies, flu, HPV, and hepatitis vaccines are examples.

**Toxoid** vaccines are retained immunogenic portions of a toxin, with removal of the whole toxin. Diphtheria, tetanus, and pertussis (DTaP or TDaP) contain toxoids against bacterial toxins.

Conjugate vaccines are some form of the pathogen's outer coating, usually a capsule of a bacterium, conjugated to a protein to increase immunogenicity. Conjugate vaccines include *Haemophilus influenzae*, *Strep. pneumo*, and *N. meningitidis*.

## Schedules for Vaccination

DO NOT MEMORIZE VACCINATION SCHEDULES. They change and are posted in every room in every office everywhere.

| LIVE ATTENUATED | KILLED | TOXOID | POLYSACCHARIDE CAPSULE |
|---|---|---|---|
| Measles | Rabies | Diphtheria | *Strep. pneumo* |
| Mumps | Flu | Tetanus | *N. meningitidis* |
| Rubella | Hep A | Pertussis | *H. influenzae* |
| Varicella | Hep B | | |
| Polio | HPV | | |
| Yellow fever | | | |
| Smallpox | | | |

**Table 13.2: Vaccine Types**